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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/527,525
Filing Date: October 14, 2005
Appellant(s): MARKOU ET AL.

Hugh Wang
(Reg. No. 47,163)
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed April 14, 2010 appealing from the Office action mailed December 15, 2009.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected in the application: claims 1-3, 6, 7, 9, 16, 27, 28 and 32. Claims 1-3, 6, 7, 9, 16, 17, 19, 27, 18 and 32 are pending. Claims 10, 14, 15, 17 and 19 are withdrawn. Claims 4, 5, 8, 11-13, 18, 20-26, 29-31 and 33 are cancelled.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

US 640794 B1	Adam et al.	6-2002
US 2003/0195139 A1	Corsi et al.	10-2003

Chiamulera et al. "Reinforcing and locomotor stimulant effects of cocaine are absent in mGluR5 null mutant mice" Nature Neuroscience, 2001, vol. 4, issue 9, pp. 873-874.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

(1) Claims 1-3, 6, 7 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adam et al. (US 6407,094 B1) in view of Corsi et al. (US 2003/0195139 A1) or Chiamulera et al. (Nature Neuroscience, 2001, vol. 4(9), pp. 873-874).

Adam et al. teaches compounds that act as Group II (i.e. mGluR 2 and 3) metaboltropic glutamate receptor antagonist (see column 16, lines 47 and 48) and treat conditions such as nicotine addiction, and opiate addiction (see column 1, lines 54-56 and column 3, lines 20-24; addresses claims 1-3, 6, 7 and 16). The antagonist can be in their pharmaceutically acceptable salts (see column 3, line 4).

Adam et al. does not teach an antagonist which modulated metabotropic glutamate receptor 5, or its administration in combination with the antagonist of Adam et al.

Corsi et al. teaches a method of treating substance dependence, wherein the substance is nicotine, opiate, cocaine, amphetamine, benzodiazepine and ethanol, comprising administering a therapeutically effective amount of an antagonist of mGluR5 (see claims 21-23; addresses claims 1-3, 6, 7 and 16). The compounds can be in the form of salts (see page 3, paragraph 55, lines 1 and 2).

Chiamulera et al. teaches the significant contribution of mGlu5 receptors to the behavioral effects of cocaine addiction (see page 873, column 1, paragraph 1, last 4 lines). A decrease of self-administration of cocaine was observed with an administration of the mGluR5 antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP); see page 873, column 2, last paragraph, lines 1-4).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Adam et al. and a combination with an antagonist which modulates metabotropic glutamate receptor 5 because of the following: (1) Adam et al., Corsi et al., and Chiamulera et al. teach methods that treat addictive disorders; (2) Adam et al. teaches the treatment of addictive disorders with a mGluR 2 and 3 antagonist; and (3) Corsi et al. and Chiamulera et al. teach the treatment of an addictive disorder with a mGluR 5 antagonist. One would be motivated to combine the two methods because although different compounds are used and antagonize different mGluR's, they both treat addictive disorders. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960); *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992); and *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987).

(2) Claims 9, 27, 28 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chiamulera et al. (Nature Neuroscience, 2001, vol. 4(9), pp. 873-874) in view of Adam et al. (US 6,407,094 B1) as applied to claims 1-3, 6, 7 and 16 above and Applicant's admitted prior art (see specification page 14, paragraph 2, lines 1 and 2, and page 16, group II, line 1 and 4).

The teachings of Chiamulera et al. and Adam et al. all are as applied to claims 1-3, 6, 7 and 16 above.

Chiamulera et al. and Adam et al. do not teach the antagonist 2S-2-amino-2-(1S,2S-2carboxycyclopropane-1-yl)-3-(xanth-9-yl)propionic acid (LY341495; claims 9 and 28). Also, the administration comprising: (a) administering to a subject in need thereof, an effective amount of at least one antagonist that modulates at least one of mGluR2, 3, and 5 (specifically LY341495 or/and MPEP) during a first time period, wherein the first time period is a time period wherein the subject expects to be in an environment wherein or exposed to stimuli in the presence of which, the subject habitually uses an addictive substance; and (b) administering at least one antagonist that modulates at least one of mGluR2 and/or 3 (specifically LY341495) during a second time period, wherein the second time period is a time period wherein the subject is suffering from withdrawal and/or depression, is not taught (claim 27). Lastly, wherein the first antagonist and the second antagonist are administered to the subject sequentially or simultaneously is also not taught (claim 32)

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Chiamulera et al. and the antagonist LY341495 because of the following: (1) both Chiamulera et. al. and Adam et al. teach methods to treat substance abuse; (2) Adam et al. teaches the treatment of an addictive disorders or depression with a mGluR 2 and 3 antagonist; and (3) LY341495 is a well known mGluR 2 and 3 antagonist in the art (indicated by the specification page 14, paragraph 2, lines 1 and 2, and page 16, group II, line 1 and 4). One would be motivated to combine the two methods because although different compounds are used and antagonize different mGluR's, they both treat substance abuse. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960); *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992); and *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Chiamulera et al. and an administration comprising: (a) administering to a subject in need thereof, an effective amount of at least one antagonist that modulates at least one of mGluR2, 3, and 5 (specifically LY341495 or/and MPEP) during a first time period, wherein the first time

period is a time period wherein the subject expects to be in an environment wherein or exposed to stimuli in the presence of which, the subject habitually uses an addictive substance; and (b) administering at least one antagonist that modulates at least one of mGluR2 and/or 3 (specifically LY341495) during a second time period, wherein the second time period is a time period wherein the subject is suffering from withdrawal and/or depression; or (c) wherein the first antagonist and the second antagonist are administered to the subject sequentially or simultaneously because without unexpected results, one skilled in the art can reasonably design the period of administration.

(10) Response to Argument

The Appellant argues that every element of the claimed invention is not taught by the prior art. Particularly, Adams et al. merely alluded to possible therapeutic uses of certain antagonist compounds for mGluR2 and mGluR3. There is neither experimental data nor plausible substantiation in Adams et al. to suggest that the compounds are indeed effective to treating drug dependence. The Examiner's position of presumed validity of the issued U.S., patent only applies to claimed invention. More importantly, the pure speculation of Adams et al. is contradictory to results from actual scientific studies that were published in peer reviewed journals. At the time of invention, several research groups have shown that agonists (not antagonists) of mGluR2/3 were able to attenuate withdrawal symptoms and to treat morphine or nicotine dependence. Further, Fundytus et al. results show a preventative effect of the antagonist, and not efficacy in treating withdrawal if the antagonist is administered after the development of dependence. Thus, the reference teaches away from combining mGluR2/3 antagonist and a mGluR5 antagonist as presently claimed.

The Examiner disagrees because first Adams et al. provides teaching that Group II mGlu receptor antagonists (see column 16, lines 47-49) have treatable indications of conditions which lead to glutamate-deficiency functions such as nicotine and opiate addiction (see column 3, lines 12 and 20-23). Thus, Adams et al. provides a motivation to try group II mGlu receptor antagonists to treat nicotine and opiate addiction.

In regards to the other art showing opposite results, the teaching of Kenny et al. can help to explain the differences. Particularly, Kenny et al. teaches on page 1075, column 1, paragraph 3, that prolonged continuous nicotine exposure increase mGluII receptor function, but repeated exposure to psychostimulants (i.e. opiates) decreased mGluII function. Thus, it is possible that chronic nicotine and psychostimulant (i.e. opiate) administration induce different alterations in glutamatergic transmission. Alternatively, this apparent discrepancy may be explained by the fact that the long-term behavioral effects of drugs of abuse are related to the dosing administration regimen. Further, although Helton et al. teaches that a mGluR II agonist treats nicotine withdrawal symptoms, Helton et al. teaches that Group II mGluR agonist decrease glutamate release (see page 1515, right column, second paragraph, last 8 lines). Helton et al. teaches that the actions of compounds such as LY354740 (the mGluR II agonist) may be altered in the nicotine-dependent animals (see page 1515, right column, last paragraph). Thus, one can not rule out suggested therapeutic teaching of Adams et al. when the effects of chronic nicotine use on mGluR agonist or nicotine modulation of glutamate excitation (i.e. regulation of glutamate release) are not known

(as taught by Helton et al., page 1515, right column, first paragraph, last four lines). As the Appellants suggested on page 12 of the Appeal Brief (see paragraph 2), one would understand that inhibition of mGluR2/3 receptors to be the action of an antagonist compound. Thus, a Group II mGluR antagonist would have the same effect as the mGluR agonist because they would both decrease glutamate release. The above arguments and teachings of Helton et al. and Kenny et al. also apply to the teachings of Vandergriff and Rasmussen. According to the Appellant (see page 12 of the Appeal Brief, second paragraph), Fundytus and Coderre, teach activation of the mGluR receptors could reduce withdrawal symptoms in human patients, which is in contradiction to the teachings of Helton et al. because Helton et al. teach that the agonist decreases glutamate release. Further, the Examiner believes that Fundytus et al. provides a means of attenuating withdrawal symptoms (i.e. reducing withdrawal symptoms) by administering the non-selective antagonist MCPG (see page 1018, column 2, discussion, lines 1-6; and page 1017, column 1, paragraph 3 in its entirety, Figure 1b). Thus, the non-selective mGluR antagonist MCCG (at receptors 1, 2, 3, and 5) was effective in treating withdrawal symptoms. Therefore, these results support the Examiner's rejections that an antagonist can be used to treat drug dependence.

> The Appellant further argues that there is no rationale for combining mGluR2/3 and mGluR5 antagonism. Additionally, the art teaches counter-intuitive actions of the Group I and Group II receptors.

The Examiner disagrees because of the Examiner's arguments given in the previous paragraph demonstrating that it would be obvious for one to try a Group II mGluR antagonist to treat opiate/nicotine dependence. From the teaching of Corsi et al., one knows that mGluR5 antagonist treat substance dependence (see claims 21-23). From the teaching of Chiamulera et al. one knows that mGlu5 receptors also treats cocaine addiction (see page 873, column 1, paragraph 1, last 4 lines and column 2, last paragraph , lines 1-4). Thus, it would be obvious to combine methods of Adams et al., Corsi et al. and Chiamulera et al. for the treatment of drug addiction/dependence.

In regards to the opposite effects of the mGluR2/3 (Group II) and mGluR5 (Group I) receptors, the art also provides teaching to motivate one to try mGluR2/3 and mGluR5 receptor antagonist to treat drug addiction/dependence. As mentioned above, Helton et al. teaches that a mGluR II agonist treats nicotine withdrawal symptoms. Helton et al. teaches that Group II mGluR agonist decrease glutamate release (see page 1515, right column, second paragraph, last 8 lines). This teaching contradicts teachings from Fundytus and Coderre, which teach activation of the mGluR receptors could reduce withdrawal symptoms in human patients. Therefore, regardless of its expected property prior art has shown different results. Helton et al. provides some guidance by the following teaching: 1) the actions of compounds such as LY354740 (the mGluR II agonist) may be altered in the nicotine-dependent animals (see page 1515, right column, last paragraph); and 2) effects of chronic nicotine use on mGluR agonist or nicotine modulation of glutamate excitation (i.e. regulation of glutamate release) are not

known (as taught by Helton et al., page 1515, right column, first paragraph, last four lines).

> The Appellant further argues that the Examiner's interpretation of Fundytus et al. in clearly incorrect. Fundytus et al. only shows that MCPG prevented development of drug dependence, but had no effect in the treatment of withdrawal symptoms that had already developed drug dependence. Thus, Fundytus et al. teaches away from invention. The current invention is directed to reducing, alleviating or eliminating withdrawal symptoms associated with cessation of substance use in subjects that have an existing addictive disorder.

The Examiner disagrees because Fundytus et al. teach that when the mGluR antagonists were administered prior to withdrawal (i.e. subject already is addicted/dependent), there was no difference between vehicle-treated rats and mGluR antagonist treated rats (see page 1018, column 1 in its entirety). On the other hand, during the 40 min withdrawal period for morphine-dependent rats, the mGluR antagonist significantly decreased the frequency of counted symptoms compared to the vehicle-treated control group (see page 1017, column 1, paragraph 3 in its entirety, Figure 1b). Thus, the non-selective mGluR antagonist MCCG (at receptors 1, 2, 3, and 5) was effective in treating withdrawal symptoms in an existing addictive/dependent disorder. Thus, this teaching further supports the Examiner that a mGluR antagonist can treat drug dependence/addiction.

> The Appellant further argues that surprising or unexpected results have been presented in this invention. Particularly, the Appellants have shown that antagonisim instead of agonism of the mGluR2/3 receptor has beneficial results, and that the combination of the mGluR2/3 antagonist

LY341495 and the mGluR5 antagonist MPEP have additive effects (see Figures 9C, 14 and 15).

The Examiner disagrees because the Examiner has already demonstrated that it would not be unexpected for an antagonist to treat drug dependence as discussed above in the previous argument paragraphs. Further, the unexpected results demonstrated in Figures 14 and 15 are not commensurate in scope of the claims. The claims are drawn to any mGlur2/3 antagonist and any mGlur5 antagonist.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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